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Disease Area Assessment: Detailed Study and Critical Market Analysis of Top Oncology Indications in US

by

VIDHI GUPTA

PG/13/071

Under the guidance of

Ms. Divya Aggarwal

Post Graduate Diploma in Hospital and Health Management

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(Completion of Dissertation from respective organization)

The certificate is awarded to

VIDHI GUPTA

In recognition of having successfully completed her
Internship in the department of

Knowledge Management

and has successfully completed her Project on

Disease Area Assessment: Detailed Study and Critical Market Analysis of Top Oncology Indications in US

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This is to certify that **Ms. VIDHI GUPTA,** a graduate student of the **Post- Graduate Diploma in Health and Hospital Management** has worked under our guidance and supervision. He/ She is submitting this dissertation titled "**Disease Area Assessment: Detailed Study and Critical Market Analysis of Top Oncology Indications in US**" at **"ZS Associates India Private Limited"** in partial fulfillment of the requirements for the award of the **Post- Graduate Diploma in Health and Hospital Management.**

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Divya Agarwal

Ms. Divya Agarwal,
Assistant Professor,
IIHMR, Delhi

Amudha 13th May 2015

Dr. Amudha Sharma
Knowledge Management Consultant,
ZS Associates India Private Limited

INTERNATIONAL INSTITUTE OF HEALTH MANAGEMENT RESEARCH, NEW DELHI

CERTIFICATE BY SCHOLAR

This is to certify that the dissertation Disease Area Assessment: Detailed Study and Critical Market Analysis of Top Oncology Indications in US and submitted by Vidhi Gupta, PG/13/071 under the supervision of Ms. Divya Aggarwal for award of Postgraduate Diploma in Hospital and Health Management of the Institute carried out during the period from 2013 to 2015 embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other Institute or other similar institution of higher learning.

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FEEDBACK FORM

Name of the Student: *Vidhi Gupta*

Dissertation Organisation: ZS Associates India Pvt. Ltd

Area of Dissertation:

Disease Area Assessment: Detailed Study and Critical Market Analysis of the Top Oncology Indications in US

The project entailed identifying the key tumors types based on various parameters and creating a detailed market analysis, including the market size, historic and projected sales, key molecular pathway and clinical trials. The main objectives were to create comprehensive decks on each tumor type which would be widely used by people in ZS as a ready reference material.

Attendance:

Regular

Objectives achieved:

- Developed a deep understanding of the oncology disease area
- Developed an effective secondary research skill
- Worked on various data sources and learnt to analyze the data along with acquiring some skills on the critical analysis of topic

Deliverables:

Decks (Power point Presentation)

Strengths:

- Good understanding of the science behind the disease
- Good verbal and written communication
- Contributes ideas to improve or develop the deliverable
- Positive and cheerful attitude

Suggestions for Improvement:

- Needs to work on time and task management
- Can be more proactive in approaching her seniors

Dr. Anindra Sharma
Consultant, KM
ZS Associates

Signature of the Officer-in-Charge/ Organisation Mentor (Dissertation)

Date: 24/4/2015
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Vidhi Gupta

PG/13/071

INTRODUCTION

The term oncology literally means a branch of science that deals with tumours and cancers. The word “onco” means bulk, mass, or tumor while “-logy” means study. Each of the cells of the body has a tightly regulated system that controls their growth, maturity, reproduction and eventual death. Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells.

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. The burden of cancer is increasing in economically developing countries as a result of population aging and growth as well as, increasingly, an adoption of cancer-associated lifestyle choices including smoking, physical inactivity, and ‘‘westernized’’ diets.

Over the next 20 years, the number of new cancer cases diagnosed annually in the United States will increase by 45 percent, from 1.6 million in 2010 to 2.3 million in 2030, with a dramatic spike in incidence predicted in the elderly and minority populations, according to research from The University of Texas M. D. Anderson Cancer Center.

Oncology drives major medicines spend in developed and pharma emerging markets and oncology represents the largest cluster of R&D activity. The following aspects make oncology unique:

Epidemiology: Global cancer prevalence rates are on the rise owing to an aging population and changing lifestyle. Prevalence data is influenced by the increased diagnosis and survival rates across the global market.

Global market analysis: The global cancer market in 2010 was valued at $54billion, an increase of 5.1% over the previous year’s sales of $51.3 billion; and is forecasted to grow at a CAGR of 6.9% from 2010-2016 reaching $81 billion in 2016.

Pipeline analysis: Oncology has become one of the major focus areas for pharmaceutical and biotechnology companies because of the high unmet need for improved treatments for multiple types of cancer. Targeted therapies are revolutionizing the paradigm of cancer treatment and are likely to be used in most cancer patients in the next 10 years. Due to high

incidence and subsequent potential for market success, breast cancer and lung cancer continue to drive high levels of R&D. Another factor that plays a major role in the growth of the cancer therapy market is the expansion of target indication. Most of the blockbuster drugs were launched for a narrow indication, and were later approved for other indications.

Competitive landscape: In 2010, the 10 leading companies of the global cancer market represented 87.1% (or $47 billion) of the total market. The combined sales accrued from these companies expanded at 5.9% for 2009-2010.

Other aspects that make oncology unique are:

- high pharmaceutical spending
- high unmet need
- Paradigm shift with treatment modality with the emergence of targeted therapies and personalized medicines.

There is immense competition in oncology. There has been a huge flood of investment going into R&D in this disease area or people are trying to market their assets in disease areas where there has not been any activity since a very long time.

As result of this competition, there are newer partnerships happening, emergence of diagnostics, newer combination therapies. Otherwise they would be competing with each other. This is definitely a new dynamic.

The top four oncology indications according to incidence and mortality by SEER (The Surveillance, Epidemiology, and End Results Program of the National Cancer Institute works to provide information on cancer statistics in an effort to reduce the burden of cancer among the U.S. population) are as follows:

Common types of cancer (Top 4)	**Estimated new cases in 2015 (Incidence)**	**Estimated deaths in 2015 (Mortality)**
Breast cancer	231,840	40,290
Lung cancer	221,200	158,040
Prostate cancer	220,800	27,540
Melanoma (skin cancer)	73,870	9,940

Table 1: Incidence and mortality of top four oncology indications in US

REVIEW OF LITERATURE

BREAST CANCER

It is cancer that develops from breast tissue. Signs of breast cancer may include a lump in the breast, a change in breast shape, dimpling of the skin, fluid coming from the nipple, or a red scaly patch of skin. In those with distant spread of the disease, there may be bone pain, swollen lymph nodes, shortness of breath, or yellow skin.

Risk factors for developing breast cancer include: female sex, obesity, lack of physical exercise, drinking alcohol,hormone replacement therapy during menopause, ionizing radiation, early age at first menstruation, having children late or not at all, and older age. About 5–10% of cases are due to genes inherited from a person's parents, including BRCA1 and BRCA2 among others. Breast cancer most commonly develops in cells from the lining of milk ducts and the lobules that supply the ducts with milk. Cancers developing from the ducts are known as ductal carcinomas, while those developing from lobules are known as lobular carcinomas. In addition, there are more than 18 other sub-types of breast cancer. Some cancers develop from pre-invasive lesions such as ductal carcinoma in situ. The diagnosis of breast cancer is confirmed by taking a biopsy of the concerning lump. Once the diagnosis is made, further tests are done to determine if the cancer has spread beyond the breast and which treatments it may respond to.

The balance of benefits versus harms of breast cancer screening is controversial. A 2013 Cochrane review stated that it is unclear if mammographic screening does more good or harm. A 2009 review for the US Preventive Services Task Force found evidence of benefit in those 40 to 70 years of age, and the organization recommends screening every two years in women 50 to 74 years old. The medications tamoxifen or raloxifene may be used in an effort to prevent breast cancer in those who are at high risk of developing it. Surgical removal of both breasts is another useful preventative measure in some high risk women. In those who have been diagnosed with cancer, a number of treatments may be used, including surgery, radiation therapy, chemotherapy, hormonal therapy and targeted therapy. Types of surgery vary from breast-conserving surgery to mastectomy. Breast reconstruction may take place at the time of surgery or at a later date. In those in whom the

cancer has spread to other parts of the body, treatments are mostly aimed at improving quality of life and comfort.

Outcomes for breast cancer vary depending on the cancer type, extent of disease, and person's age. Survival rates in the developed world are high, with between 80% and 90% of those in England and the United States alive for at least 5 years. In developing countries survival rates are poorer. Worldwide, breast cancer is the leading type of cancer in women, accounting for 25% of all cases. In 2012 it resulted in 1.68 million cases and 522,000 deaths. It is more common in developed countries and is more than 100 times more common in women than in men.

LUNG CANCER

It also known as carcinoma of the lung or pulmonary carcinoma is a malignant lung tumor characterized by uncontrolled cell growth in tissues of the lung.

If left untreated, this growth can spread beyond the lung by process of metastasis into nearby tissue or other parts of the body. Most cancers that start in the lung, known as primary lung cancers, are carcinomas that derive from epithelialcells. The main primary types are small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). The most common symptoms are coughing (including coughing up blood), weight loss, shortness of breath, and chest pains.

The vast majority (80–90%) of cases of lung cancer are due to long-term exposure to tobacco smoke. About 10–15% of cases occur in people who have never smoked. These cases are often caused by a combination of genetic factors and exposure to radon gas, asbestos, or other forms of air pollution, including second-hand smoke. Lung cancer may be seen on chest radiographs and computed tomography (CT) scans. The diagnosis is confirmed by biopsy which is usually performed by bronchoscopy or CT-guidance.

Treatment and long-term outcomes depend on the type of cancer, the stage (degree of spread), and the person's overall health, measured by performance status. Common treatments include surgery, chemotherapy, andradiotherapy. NSCLC is sometimes treated with surgery, whereas SCLC usually responds better to chemotherapy and radiotherapy. Overall, 16.8% of people in the United States diagnosed with lung

cancer survive five years after the diagnosis, while outcomes on average are worse in the developing world. Worldwide, lung cancer is the most common cause of cancer-related death in men and women, and was responsible for 1.56 million deaths annually, as of 2012.

PROSTATE CANCER

It also known as carcinoma of the prostate is the development of cancer in the prostate, a gland in the male reproductive system. Most prostate cancers are slow growing; however, some grow relatively fast. The cancer cells may spread from the prostate to other parts of the body, particularly the bones and lymph nodes. It may initially cause no symptoms. In later stages it can cause difficulty urinating, blood in the urine, or pain in the pelvis, back or when urinating. A disease known as benign prostatic hyperplasia may produce similar symptoms. Other late symptoms may include feeling tired due to low levels of red blood cells.

Factors that increase the risk of prostate cancer include: older age, a family history of the disease, and race. About 99% of cases occur in those over the age of 50. Having a first degree relative with the disease increases the risk 2 to 3 fold. In the United States it is more common in the African American population than the Caucasian population. Other factors that may be involved include a diet high in processed meat, red meat, or milk products or low in certain vegetables. Prostate cancer is diagnosed by biopsy. Medical imaging may then be done to determine if the cancer has spread to other parts of the body.

Prostate cancer screening is controversial. Prostate-specific antigen testing increases cancer detection but does not decrease mortality. The United States Preventive Services Task Force recommends against screening using the PSA testing, due to the risk of over-diagnosis and over-treatment as most cancer diagnosed would remain asymptomatic. The USPSTF concludes that the potential benefits of testing do not outweigh the expected harms. While 5α-reductase inhibitors appear to decrease low grade cancer risk they do not affect high grade cancer risk and thus are not recommended for prevention. Supplementation with vitamins or minerals do not appear to affect the risk.

Many cases can be safely followed with active surveillance or watchful waiting. Other treatments may include a combination of surgery, radiation therapy, hormone therapy or chemotherapy. When it only occurs inside the prostate it may be curable. In those in whom the disease has spread to the bones, pain medications, bisphosphonates and

targeted therapy, among others may be useful. Outcomes depend on a person's age and other health problems as well as how aggressive and extensive the cancer is. Most people with prostate cancer do not end up dying from the disease. The five year survival rate in the United States is 99%. Globally it is the second most common type of cancer and the fifth leading cause of cancer-related death in men. In 2012 it occurred in 1.1 million men and caused 307,000 deaths. It was the most common cancer in males in 84 countries, occurring more commonly in the developed world. Rates have been increasing in the developing world. Detection increased significantly in the 1980s and 1990s in many areas due to increased PSA testing. Studies of males who died from unrelated causes have found prostate cancer in 30% to 70% of those over age 60.

MELANOMA

It is a type of skin cancer which forms from melanocytes (pigment-containing cells in the skin). In women, the most common site is the legs, and in men, the back. It is particularly common among Caucasians, especially northern Europeans and northwestern Europeans, living in sunny climates. There are higher rates in Oceania, North America, Europe, Southern Africa, and Latin America. This geographic pattern reflects the primary cause, ultraviolet light (UV) exposure in conjunction with the amount of skin pigmentation in the population. Melanocytes produce the dark pigment, melanin, which is responsible for the color of skin. These cells predominantly occur in skin, but are also found in other parts of the body, including the bowel and the eye (see uveal melanoma). Melanoma can originate in any part of the body that contains melanocytes.

The treatment includes surgical removal of the tumor. If melanoma is found early, while it is still small and thin, and if it is completely removed, then the odds of a cure are high. The likelihood that the melanoma will come back or spread depends on how deeply it has gone into the layers of the skin. For melanomas that come back or spread, treatments include chemo- and immunotherapy, or radiation therapy. Five year survival rates in the United States are on average 91%.

Melanoma is less common than other skin cancers. However, it is much more dangerous if it is not found in the early stages. It causes the majority (75%) of deaths related to skin cancer. Globally, in 2012, melanoma occurred in 232,000 people and resulted in 55,000

deaths. Australia and New Zealand have the highest rates of melanoma in the world. It has become more common in the last 20 years in areas that are mostly Caucasian.

COMMON TERMINOLOGIES

- **Incidence:** It is a measure of the probability of occurrence of a given medical condition in a population within a specified period of time. Although sometimes loosely expressed simply as the number of new cases during some time period, it is better expressed as a proportion or a rate with a denominator. Incidence is the number of new cases of a condition, symptom, death, or injury that develop during a specific time period, such as a year. Incidence shows the likelihood that a person in that population will be affected by the condition.
- **Incidence proportion**: (also known as cumulative incidence) is the number of new cases within a specified time period divided by the size of the population initially at risk.
- **Incidence rate:** It is the number of new cases per population at risk in a given time period. When the denominator is the sum of the person-time of the at risk population, it is also known as the incidence density rate or person-time incidence rate.
- **Median Age at Diagnosis/Death:** The age at which half of all reported cases were older and half were younger.
- **Five-Year Survival Rate:** The percentage of people in a study or treatment group who are alive five years after they were diagnosed with or treated for a disease, such as cancer. The disease may or may not have come back.
- **Age-Adjusted Rate:** A statistical method allowing comparisons of populations that takes into account age-distribution differences between populations. Most incidence and death data in SEER are age-adjusted, although some tables, in contrast, present the crude rate. Age-adjusting takes the 2000 US population distribution and applies it to other time periods under consideration. This assures that such rates do not reflect any changes in the population age distribution. Rates can be adjusted for the distribution of other characteristics such as race/ethnicity.
- **Mortality:** The number of deaths from cancer during a specific time period.

- **SEER:** The Surveillance, Epidemiology, and End Results (SEER) Program of the NCI is a collection of central cancer registries in the United States that collect and submit cancer incidence, prevalence, mortality, survival, stage at diagnosis data and other statistics to the National Cancer Institute. The National Cancer Act of 1971 mandated the collection, analysis, and dissemination of data useful in the prevention, diagnosis, and treatment of cancer leading to the establishment of the SEER Program.
- **Stage:** Stage provides a measure of disease progression, detailing the degree to which the cancer has advanced. Two methods commonly used to determine stage are AJCC and SEER historic. The AJCC method is more commonly used in the clinical settings, while SEER has standardized and simplified staging to ensure consistent definitions over time SEER describes cancers in five stages:

  - **In situ cancer** is early cancer that is present only in the layer of cells in which it began.
  - **Localized cancer** is cancer that is limited to the organ in which it began, without evidence of spread.
  - **Regional cancer** is cancer that has spread beyond the original (primary) site to nearby lymph nodes or organs and tissues.
  - **Distant cancer** is cancer that has spread from the primary site to distant organs or distant lymph nodes
  - **Unstaged cancer** is cancer for which there is not enough information to indicate a stage.
- **Staging systems** (http://www.cancer.org/treatment/understandingyourdiagnosis/staging)

There are different types of staging systems, but the most common and useful staging system for most types of cancers is the TNM system.

- **The TNM system:** The American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) maintain then classification system as a tool for doctors to stage different types of cancer based on certain standards. It's updated every 6 to 8 years to include advances in our understanding of cancer.

In the TNM system, each cancer is assigned a letter or number to describe the tumor, node, and metastases.

T stands for the original (primary) tumor.

N stands for nodes. It tells whether the cancer has spread to the nearby lymph nodes

M stands for metastasis. It tells whether the cancer has spread to distant parts of the body

The T category gives information about aspects of the original (primary) tumor, such as its size, how deeply it has grown into the organ it started in, and whether it has grown into nearby tissues.

- TX means the tumor can't be measured.
- T0 means there is no evidence of a primary tumor (it cannot be found).
- This means that the cancer cells are only growing in the most superficial layer of tissue, without growing into deeper tissues. This may also be called in situ cancer or pre-cancer.

Numbers after the T (such as T1, T2, T3, and T4) might describe the tumor size and/or amount of spread into nearby structures. The higher the T number, the larger the tumor and/or the more it has grown into nearby tissues.

The N category describes whether the cancer has spread into nearby lymph nodes.

- NX means the nearby lymph nodes cannot be evaluated.
- N0 means nearby lymph nodes do not contain cancer.

Numbers after the N (such as N1, N2, and N3) might describe the size, location, and/or the number of nearby lymph nodes affected by cancer. The higher the N number, the greater the cancer spread to nearby lymph nodes.

The M category tells whether the cancer has spread (metastasized) to distant parts of body).

- M0 means that no distant cancer spread was found.
- M1 means that the cancer has spread to distant organs or tissues (distant metastases were found).

Most cancer types have their own version of this classification system, so letters and numbers don't always mean the same thing for every kind of cancer. For example, in some types of cancer, the T categories describe the size of the main tumor, while in others they describe how deeply the tumor has grown in to the organ it started in, or whether the tumor has grown into nearby structures (regardless of its size).

- **PSA Test:** Prostate-specific antigen, or PSA, is a protein produced by cells of the prostate gland. The PSA test measures the level of PSA in a man's blood. For this test, a blood sample is sent to a laboratory for analysis. The results are usually reported as nanograms of PSA per milliliter(ng/mL) of blood.

The blood level of PSA is often elevated in men with prostate cancer, and the PSA test was originally approved by the FDA in 1986 to monitor the progression of prostate cancer in men who had already been diagnosed with the disease. In 1994, the FDA approved the use of the PSA test in conjunction with a digital rectal exam (DRE) to test asymptomatic men for prostate cancer. Men who report prostate symptoms often undergo PSA testing (along with a DRE) to help doctors determine the nature of the problem.

In addition to prostate cancer, a number of benign (not cancerous) conditions can cause a man's PSA level to rise. The most frequent benign prostate conditions that cause an elevation in PSA level are prostatitis (inflammation of the prostate) and benign prostatic hyperplasia (BPH) (enlargement of the prostate). There is no evidence that prostatitis or BPH leads to prostate cancer, but it is possible for a man to have one or both of these conditions and to develop prostate cancer as well.

- **Gleason Score:** It is a system of grading prostate cancer tissue based on how it looks under a microscope. It ranges from 2 to 10 and indicates how likely a tumor will spread. Gleason score is obtained by assigning a primary grade to the most predominant grade present and a secondary grade to the second most predominant grade, and adding the two. The lower the grade, the tumor is less likely to spread.
- **Clinical Trials:** Clinical trials are conducted to collect data regarding the safety and efficacy of new drug and device development. There are several steps and stages of approval in the clinical trials process before a drug or device can be sold in the consumer market, if ever.

Drug and device testing begins with extensive laboratory research which can involve years of experiments in animals and human cells. If the initial laboratory research is successful, researches send the data to the Food and Drug Administration (FDA) for approval to continue research and testing in humans.

Once approved, human testing of experimental drugs and devices can begin and is typically conducted in four phases. Each phase is considered a separate trial and, after completion of a phase, investigators are required to submit their data for approval from the FDA before continuing to the next phase.

Human Clinical Trial Phases: (http://www.cancer.net/navigating-cancer-care/how-cancer-treated/clinical-trials/phases-clinical-trials)

- **Phase I** studies assess the safety of a drug or device. This initial phase of testing, which can take several months to complete, usually includes a small number of healthy volunteers (20 to 100), who are generally paid for participating in the study. The study is designed to determine the effects of the drug or device on humans including how it is absorbed, metabolized, and excreted. This phase also investigates the side effects that occur as dosage levels are increased. About 70% of experimental drugs pass this phase of testing.
- **Phase II** studies test the efficacy of a drug or device. This second phase of testing can last from several months to two years, and involves up to several hundred patients. Most phase II studies are randomized trials where one group of patients receives the experimental drug, while a second "control" group receives a standard treatment or placebo. Often these studies are "blinded" which means that neither the patients nor the researchers know who has received the experimental drug. This allows investigators to provide the pharmaceutical company and the FDA with comparative information about the relative safety and effectiveness of the new drug. About one-third of experimental drugs successfully complete both Phase I and Phase II studies.
- **Phase III** studies involve randomized and blind testing in several hundred to several thousand patients. This large-scale testing, which can last several years, provides the pharmaceutical company and the FDA with a more thorough understanding of the effectiveness of the drug or device, the benefits and the range of possible adverse reactions. 70% to 90% of drugs that enter Phase III studies successfully complete this

phase of testing. Once Phase III is complete, a pharmaceutical company can request FDA approval for marketing the drug.

- **Phase IV** studies, often called Post Marketing Surveillance Trials, are conducted after a drug or device has been approved for consumer sale. Pharmaceutical companies have several objectives at this stage: (1) to compare a drug with other drugs already in the market; (2) to monitor a drug's long-term effectiveness and impact on a patient's quality of life; and (3) to determine the cost-effectiveness of a drug therapy relative to other traditional and new therapies. Phase IV studies can result in a drug or device being taken off the market or restrictions of use could be placed on the product depending on the findings in the study.

➢ **Commonly used primary endpoints for clinical trial:**

- **Overall Survival:** Overall survival is defined as the time from randomization until death from any cause, and is measured in the intent-to-treat population. Survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. This endpoint is precise and easy to measure, documented by the date of death. Bias is not a factor in endpoint measurement. Survival improvement should be analyzed as a risk-benefit analysis to assess clinical benefit.
- **Disease Free Survival:** Generally, DFS is defined as the time from randomization until recurrence of tumor or death from any cause. The most frequent use of this endpoint is in the adjuvant setting after definitive surgery or radiotherapy. DFS also can be an important endpoint when a large percentage of patients achieve complete responses with chemotherapy. Although overall survival is a conventional endpoint for most adjuvant settings, DFS can be an important endpoint in situations where survival may be prolonged, making a survival endpoint impractical. DFS has been the primary basis of approval for adjuvant breast cancer hormonal therapy, adjuvant colon cancer, and adjuvant cytotoxic breast cancer therapy. Compared with standard cytotoxic therapies, hormonal therapies carry minimum side effects and thus a favorable risk-benefit relationship. DFS can be a surrogate for clinical benefit or it can provide direct evidence of clinical benefit. This determination is based on the magnitude of the effect, its risk-benefit relationship, and the disease setting. However, in disease settings where survival

benefit has been already established, it is unlikely that DFS can be considered a clinical benefit.

In cancer, the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. In a clinical trial, measuring the disease-free survival is one way to see how well a new treatment works. Also called DFS, relapse-free survival, and RFS.

- **Objective Response Rate:** ORR is defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period. Response duration usually is measured from the time of initial response until documented tumor progression. Generally, the FDA has defined ORR as the sum of partial responses plus complete responses. When defined in this manner, ORR is a direct measure of drug antitumor activity, which can be evaluated in a single-arm study. Stable disease should not be a component of ORR. Stable disease can reflect the natural history of disease, whereas tumor reduction is a direct therapeutic effect.
- **Progression Free Survival:** PFS is defined as the time from randomization until objective tumor progression or death. The precise definition of tumor progression is important and should be carefully detailed in the protocol.
- **Time to Progression:** TTP and PFS have served as primary endpoints for drug approval. TTP is defined as the time from randomization until objective tumor progression; TTP does not include deaths.

METHODOLOGY

Aim and Objectives

General Objective: The aim of the study is to carry out a detailed disease area assessment of each of the below mentioned indication, namely:

- Breast cancer
- Lung cancer
- Prostate cancer
- Melanoma (skin cancer)

Specific Objectives:

- To derive scientific insights of the above mentioned oncology indications.
- To ascertain the market dynamics of each of the diseases mentioned.
- To determine the competitive landscape for each of these cancers.

Research Procedure

This project is a secondary research based project. Following information is captured to carry out a detailed study for each of the cancers:

- Epidemiology of disease
- Classification of disease
- Treatment pathway for disease
- List of products (marketed and pipeline)
- Product comparison of marketed products
- US indication sales for the indication and market share by product
- Key clinical trials
- Competitive milestone
- Pricing of the marketed products

This information is obtained from various data sources, some of them are freely available on the internet (public data sources) and some are subscribed (paid) data sources (by the organisation). Following is a list of few data sources that provide this kind of information.

Public Data Sources	
Data Source	**Type of Information**
Clinicaltrial.gov	Clinical trial details
	Purpose of the trial
	Study design of the trial
	Study start date, estimated duration, location of trial, criteria for trial
SEER	Incidence (age adjusted rates), diagnosis rate
	Mortality (age adjusted rates, race),
	Trends in incidence and mortality
	Survival rates and staging
Product Labels (drugs@fda)	Drug details
	Clinical studies detail
	Dosage and administration
	Adverse reactions
	Pharmacology
NCCN Guidelines	Treatment flow
	Recommended products
cancer.org, cancer.gov, Medscape, Epocrates	Classification of disease
	Treatment algorithm
	Epidemiology
	Available products
Decision Resource	Overall survival rates
	Efficacy of current standard care
	Serious adverse events

Table 2: Public Data Sources

Subscribed Data Sources	
Data Source	**Type of Information**
Adis R&D Insights	Drugs details
	Trial phase
	Patent information
	Therapeutic class
	Mechanism of action
	Organisation details
	Indication/ phase of development/ location
Data Monitor	Drug details
	Stage of development, launch year, primary patent expiry
	Sales analysis
	Data monitor reports
Evaluate Pharma	Drug details
	Launch dates
	Patent expiry
	US sales, worldwide sales (historical, projected)
	Phase of development
Rx Price Verify	Prices
	Dosage
Bloomberg	New/ total prescription sales
	Company analysis
	Industry profiles
	Drug profiles

Table 3: Subscribed Data Sources

FINDINGS AND ANALYSIS

BREAST CANCER

US Epidemiology:

Parameter	Data
Estimated incidence (2014)	231,840
Estimated mortality (2014)	40,290
Median age at diagnosis	61 yrs
Median age at death	68 yrs
Age adjusted incidence rates (2011)	124.6/100,000 women/yr
Age adjusted death rates (2011)	22.2/100,000 women/yr
Overall 5 year survival (2004-2010)	89.2%

Table 4: Breast Cancer Epidemiology

Types of Classification of Breast Cancer:

1. Based on stage of diagnosis:

Stage	Stage distribution	5-yr survival rate (%)
Localized	61%	98.5%
Regional	32%	84.6%
Distant	5%	25%
Unknown	2%	49.8%

Table 5: Breast Cancer Classification

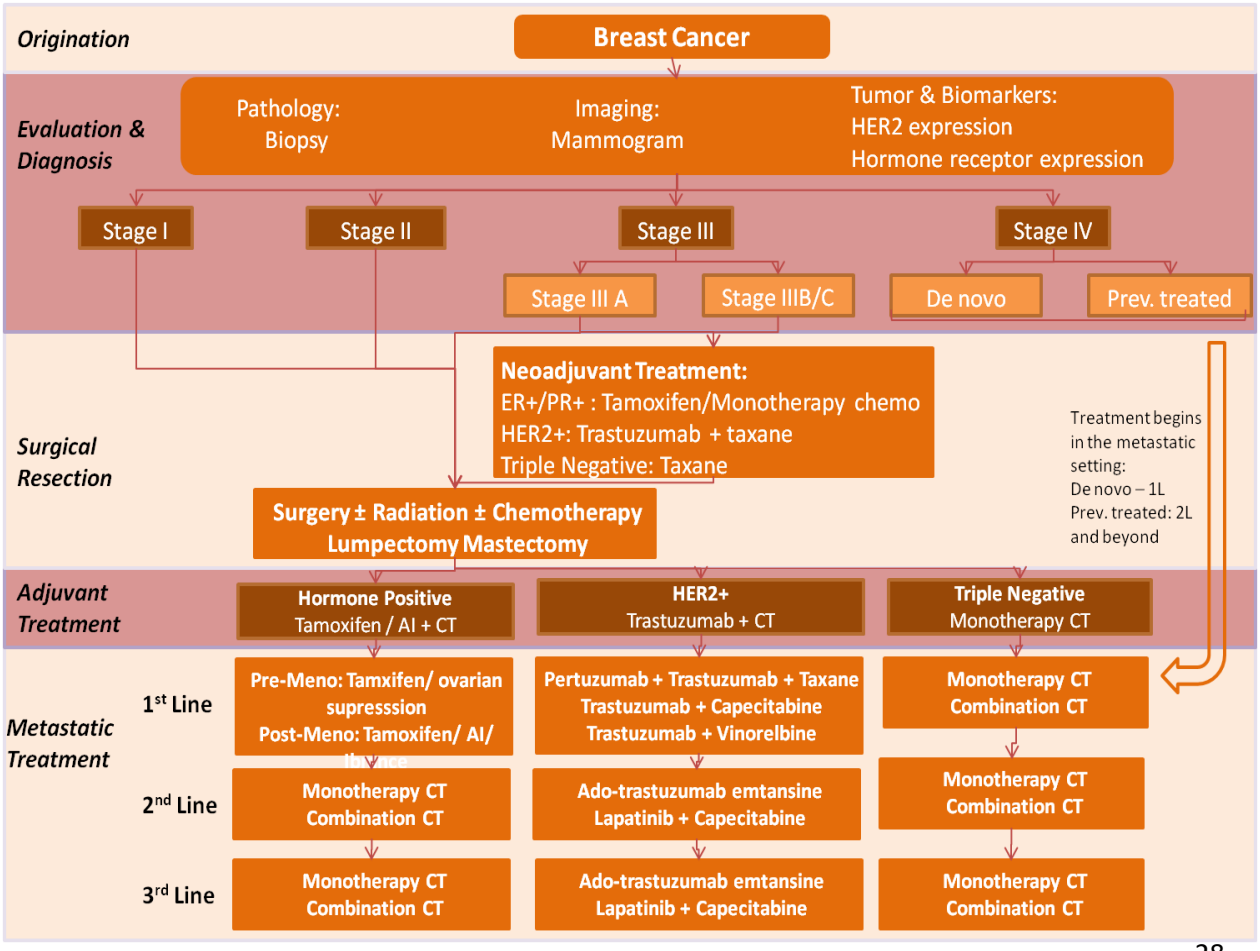
2. Based on anatomic stage: (on the basis of TNM staging of cancer)
    - Stage I
    - Stage II
    - Stage III
    - Stage IV

3. Based on driver mutations:
    - ER overexpression

- PR overexpression
- PIK3CA
- HER2+ overexpression
- FGFR 1
- PTEN
- AKT 1

4. Based on genome project:
    - Luminal A (Hormone positive/ HER2 negative)
    - Luminal B (Hormone positive/ HER2 positive)
    - HER2+ only (HER2 positive only)
    - Basal like (Hormone negative/ HER2 negative)
    - Others

Treatment Flow:



Monotherapy CT : Doxorubicin, Paclitaxel, Capecitabine, Gemcitabine, Vinorelbine, Eribulin
Combination CT: FAC (5-fluorouracil, doxorubicin), FEC (5-fluorouracil, epirubicin, cyclophosphamide), AC (doxorubicin, cyclophosphamide), CMF (cyclophosphamide, methotraxate, 5-fluorouracil) ,GT (gemcitabine, paclitaxel) AI : aromatase inhibitors

Figure 1: Breast Cancer Treatment Flow

Sales and Market Share by Product:

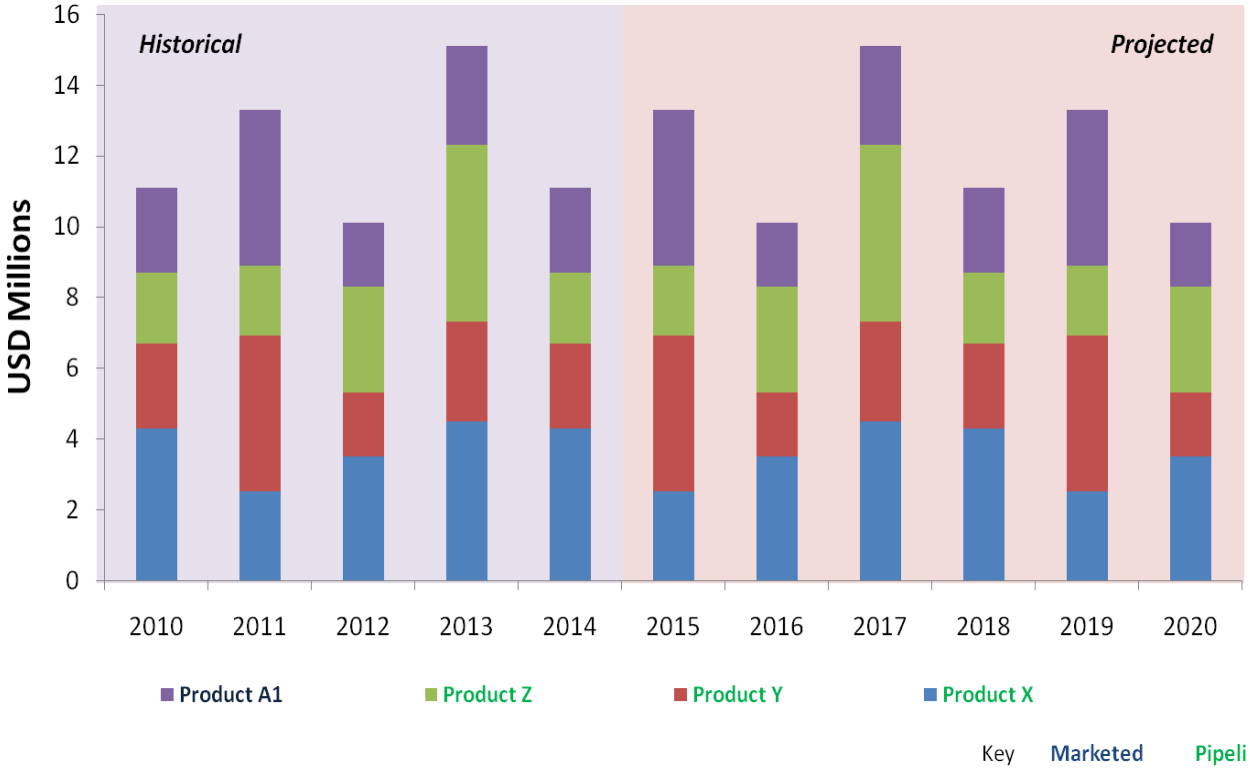


Figure 2: US Sales and Market Share by Product

With the help of this graph, one is able to identify the market situation for the indication, historically and futuristically. It helps in recognizing the products that are currently the market leaders and which ones will be frontrunners in the coming times and which products will experience stiff competition and shall show decrease in sales. It also gives an idea of how the market will grow and approximately at what rate (compound annual growth rate), which product will have a higher market share and how the market was and will be distributed among various products.

List of Products:

Marketed		
Product	**Mechanism of Action**	**Company**
Herceptin (trastuzumab)	Anti HER2 monoclonal antibody	Roche
Perjeta (pertuzumab)	HER2 dimerisation inhibtors	Roche
Kadcyla (ado-trastuzumab emtansine)	Anti HER2 antibody drug conjugate	Roche
Tykerb (lapatinib)	Dual tyrosine kinase inhibitors	GSK
Afinitor (everolimus)	mTOR inhibitors	Novartis
Ibrance (palbociclib)	Cyclin D Kinase 4/6 Inhibitors	Pfizer

Table 6: List of Marketed Products for Breast Cancer

Pipeline		
Product	**Mechanism of Action**	**Company**
Glembatumumab vedotin	Anti GPNMB antibody drug conjugate	Celldex
Neratinib	Dual tyrosine kinase inhibitors	Puma Biotech
Afatinib	Dual tyrosine kinase inhibitors	BI
Buparlisib	PI3K inhibitors	Novartis
Abemaciclib	Cyclin D Kinase 4/6 Inhibitors	Eli Lilly
Ribociclib	Cyclin D Kinase 4/6 Inhibitors	Pfizer
Olaparib	PARP Inhibitors	AstraZeneca
Veliparib	PARP Inhibitors	AbbVie
Niraparib	PARP Inhibitors	Tesaro, Inc

Table 7: List of Pipeline Products for Breast Cancer

Clinical Product Comparison – Drugs available in the market:

		Herceptin *(trastuzumab)*	Perjeta *(pertuzumab)*	Kadcyla *(ado-trastuzumab emtansine)*	Ibrance *(palbociclib)*	Tykerb *(lapatinib)*
Indication	1L	Adjuvant,Metastatic	Neoadjuvant, Metastatic		Metastatic (HR+ & HER2-)	Metastatic
	2L	Adjuvant,Metastatic	Metastatic	Metastatic		Metastatic
	3L	Adjuvant,Metastatic		Metastatic		Metastatic
MOA		Immunomodulator	HER2 dimerisation inhibitors	Antibody drug conjugate	Cyclin dependent kinase (CDK) 4&6 inhibitors	Tyrosine kinase inhibitors
Efficacy	OS	25.1 months	56.5 months	30.9 months		18 months
	PFS		18.5 months	9.6 months	20.2 months	10 months
	TTP	7.2 months				23.9 monhs
	ORR	39.5%	80.2%	43.6%		31l.8%
	MRD	8.3 months	20.2 months			
Risk Factors		***Black box warning*** • Pulmonary toxicity • Embryo-fetal toxicity	***Black box warning*** • Neutropenia • Embryo-fetal toxicity • Peripheral neuropathy	***Black box warning*** • Hepatotoxicity • Cardiotoxicity • Neuropathy • Pulmonary toxicity	• Neutropenia • Embryo-fetal toxicity	***Black box warning*** • Hepatotoxicity • Embryo-fetal toxicity • Pneumonitis

		Adriamycin *(doxorubicin)*	Taxol *(paclitaxel)*	Taxotere *(docetaxel)*	Abraxane *(protein bound paclitaxel)*	Xeloda *(capecitabine)*
Indication	1L	Adjuvant,Metastatic	Adjuvant,Metastatic	Adjuvant,Metastatic		
	2L	Adjuvant,Metastatic	Adjuvant,Metastatic	Adjuvant,Metastatic	Metastatic	Metastatic
	3L	Adjuvant,Metastatic	Adjuvant,Metastatic	Adjuvant,Metastatic	Metastatic	Metastatic
MOA		DNA intercalation	Microtubule stabilizer	Microtubule stabilizer	Tubulin inhibitor	Thymidylate synthase inhibitors
Efficacy	OS	9 months	11,7 months	11.4 months		14 months
	PFS					6 months
	TTP		4.2 months	4.3 months		22-32%
	ORR		28%	28.1%		
	MRD					
Risk Factors		***Black box warning*** • Cardiomyopathy • Secondary mailgnancies • Tissue necrosis	***Black box warning*** • Neutropenia • Bone marrow suppression • Peripheral neuropathy	***Black box warning*** • Neutropenia • Hepatotoxicity • Fluid retention	***Black box warning*** • Myalgia • Myelosuppression • Neuropathy	• Diarrhea • Cardiotoxicity • Anticougulation response varies

OS: overall survival, PFS: progression free survival, TTP: time to pregression, ORR: objective response rate, MRD: median response duration

Figure 3: Breast Cancer Product Comparison

Identification of Key Clinical Trials:

Trial Name	Company	Patient Population	Key Comparators	Primary Endpoints	Expected Primary completion date
BOLERO – 3 (Afinitor – Ph III)	Novartis	2L,HER2+ locally advanced or pre-treated metastatic breast cancer	Afinitor + Vinorelbine + Trastuzumab	Progression free survival	Jun 2015
			Vinorelbine + Trastuzumab		
BOLERO – 1 (Afinitor – Ph III)		2L,HER2+ locally advanced or metastatic breast cancer	Afinitor + Paclitaxel + Trastuzumab	Progression free survival	Dec 2015
			Paclitaxel + Trastuzumab		
BELLE – 2 (Buparlisib – Ph III)		2L, HR+, HER2-, metastatic breast cancer	Buparlisib + Fluvestrant	Progression free survival	Sep 2017
			Fluvestrant		
NALA (Neratinib – Ph III)	Puma Biotechnology	3L, HER2+ breast cancer	Neratinib + Capecitabine	Overall survival	May 2018
			Lapatinib + Capecitabine		
OlympiA (Olaparib – Ph III)	AstraZeneca	Adjuvant,BRCA+, HER2- breast cancer	Olaparib	Disease free survival	Mar 2020
			placebo		
OlympiAD (Olaparib – Ph III)		BRCA+, HER2- metastatic breast cancer	Olaparib monotherapy	Progression free survival	May 2016
			Standard therapy		
BRAVO (Niraparib – Ph III)	Tesaro,Inc.	BRCA+, HER2- metastatic breast cancer	Niraparib	Progression free survival	Dec 2015
			Physicians choice therapy		
MONARCH 2 (Abemaciclib – Ph III)	Eli Lilly and Company	ER+, HER2- advanced breast cancer	Abemaciclib + Fluvestrant	Progression free survival	Feb 2017
			Fluvestrant		
Veliparib – Ph III	AbbVie	BRCA+, HER2- metastatic breast cancer	Veliparib + Carboplatin + Paclitaxel	Progression free survival	Jan 2017
			Carboplatin + Paclitaxel		

Figure 4: Breast Cancer Key Clinical Trials

Competitive milestone:

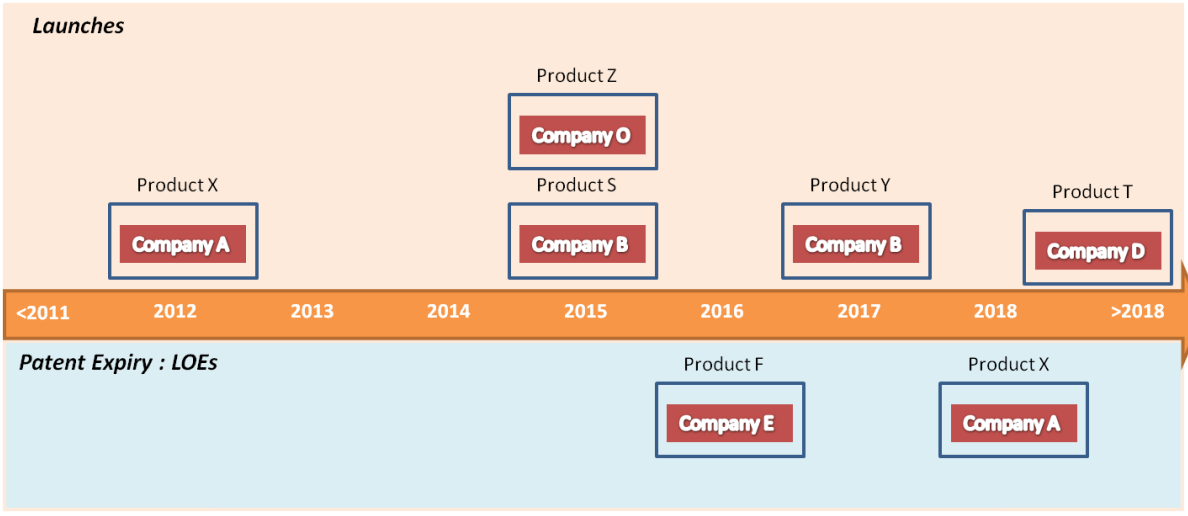


Figure 5: Competitive Milestone

With the help of competitive milestone, one aims to identify the launch dates of the products in the pipeline in the coming 3-4 years and also the launch dates of the products already in the market. Also, it gives information regarding the patent expiry of the available products so as to give an idea that when a product will lose its exclusivity and thus affecting the overall market and the products' status in the market. Competitive milestone provides an insight as to how competitive the market for this indication has been and how it is expected to be in the near future.

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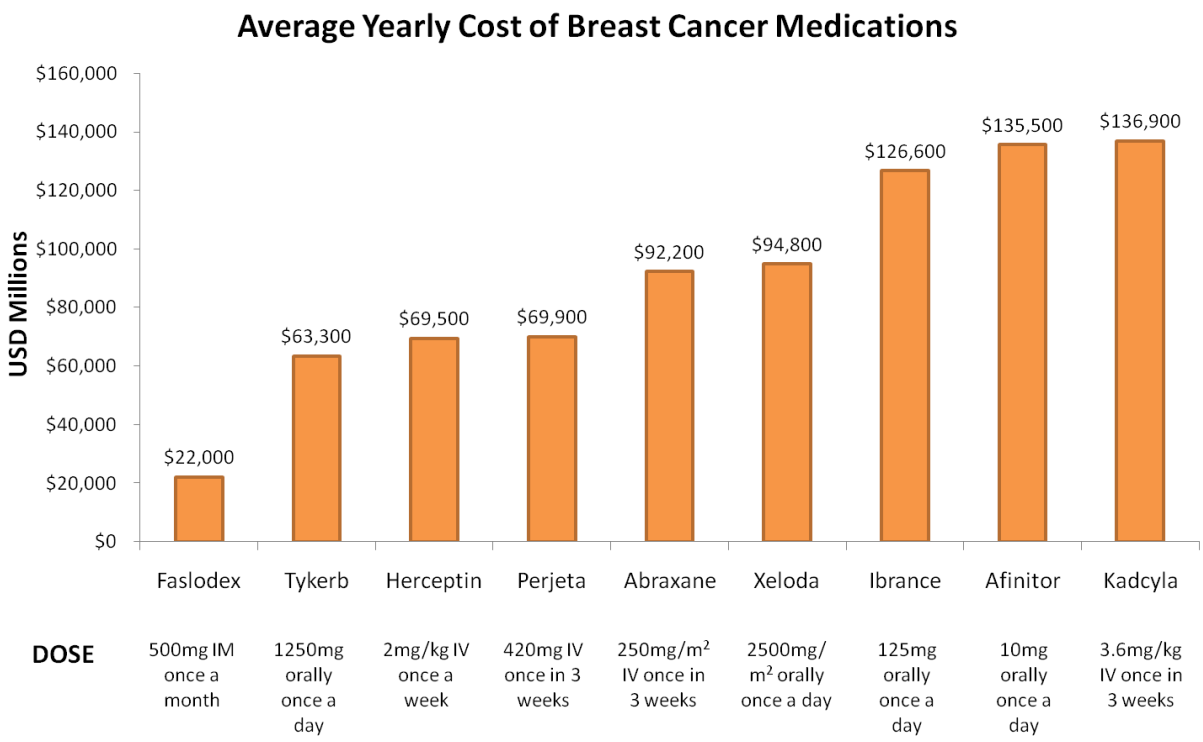

Figure 6: Average Yearly Cost of Breast Cancer Medication

LUNG CANCER

US Epidemiology

Parameter	Data
Estimated incidence (2014)	221,200
Estimated mortality (2014)	158,040
Median age at diagnosis	70 yrs
Median age at death	72 yrs
Age adjusted incidence rates (2011)	60.1/100,000/yr
Age adjusted death rates (2011)	48.4/100,000/yr
Overall 5 year survival (2004-2010)	16.8%

Table 8: Lung Cancer Epidemiology

Types of Classification of Lung Cancer:

5. Based on histology:
    - Small cell lung cancer (SCLC)
        i. Small cell/ oat cell
        ii. Combined small cell
    - Non small cell lung cancer (NSCLC)
        i. Squamous cell
        ii. Non squamous cell
            1. Adenocarcinoma
            2. Large cell carcinoma
    - Others
6. Based on stage of diagnosis - NSCLC:

Stage	Stage distribution	5-yr survival rate (%)
Localized	15%	54%
Regional	22%	26.5%
Distant	57%	4.0%
Unknown	6%	7.4%

Table 9: Lung Cancer Classification

1. Based on stage of diagnosis - SCLC:
    - Limited stage disease
    - Extensive stage disease

2. Based on driver mutation:
    - KRAS
    - EGFR
    - ALK
    - HER2
    - BRAF
    - PIK3CA
    - MET
    - NRAS

Treatment Flow - NSCLC:

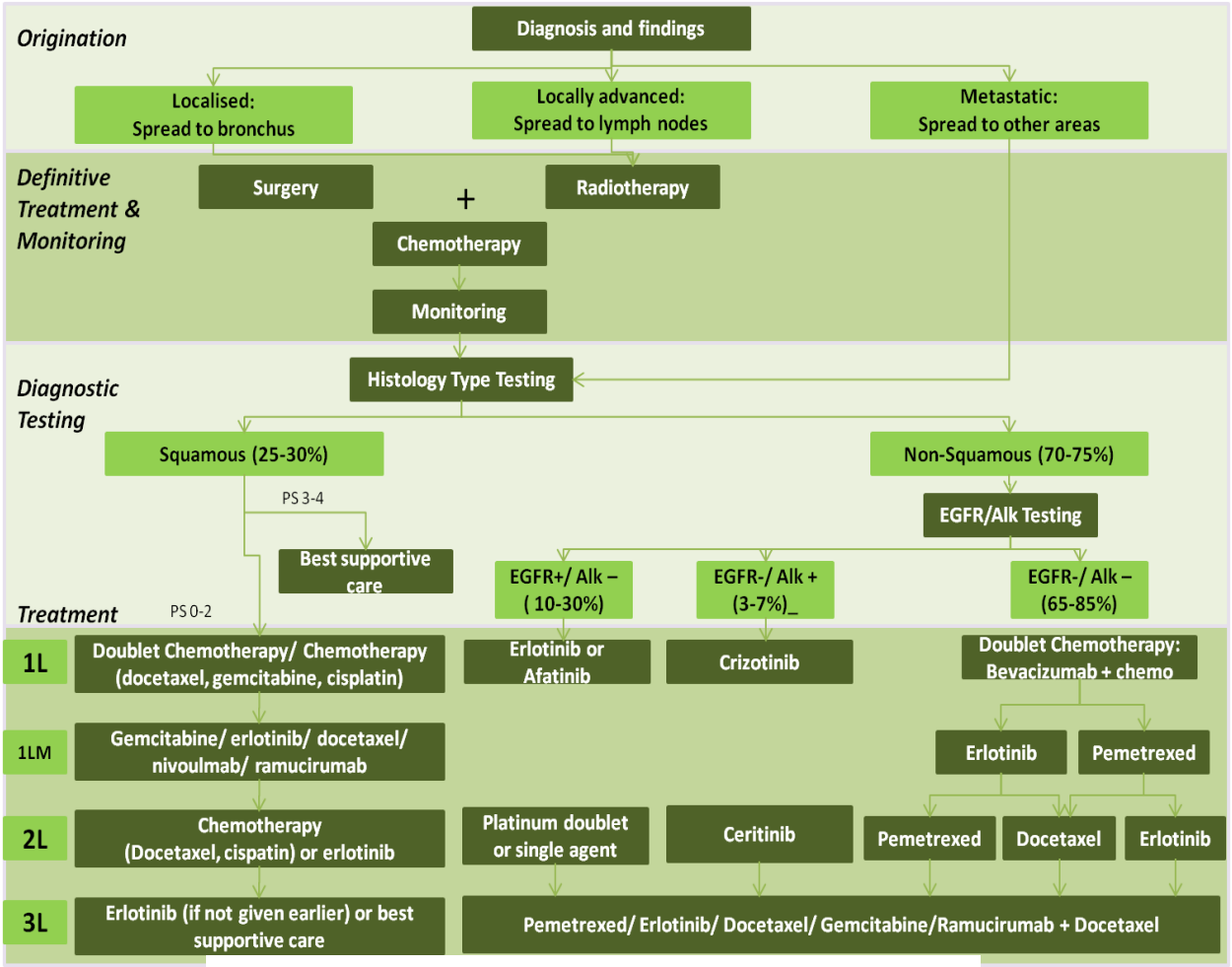

Figure 7: NSCLC Treatment Flow

Treatment Flow – SCLC:

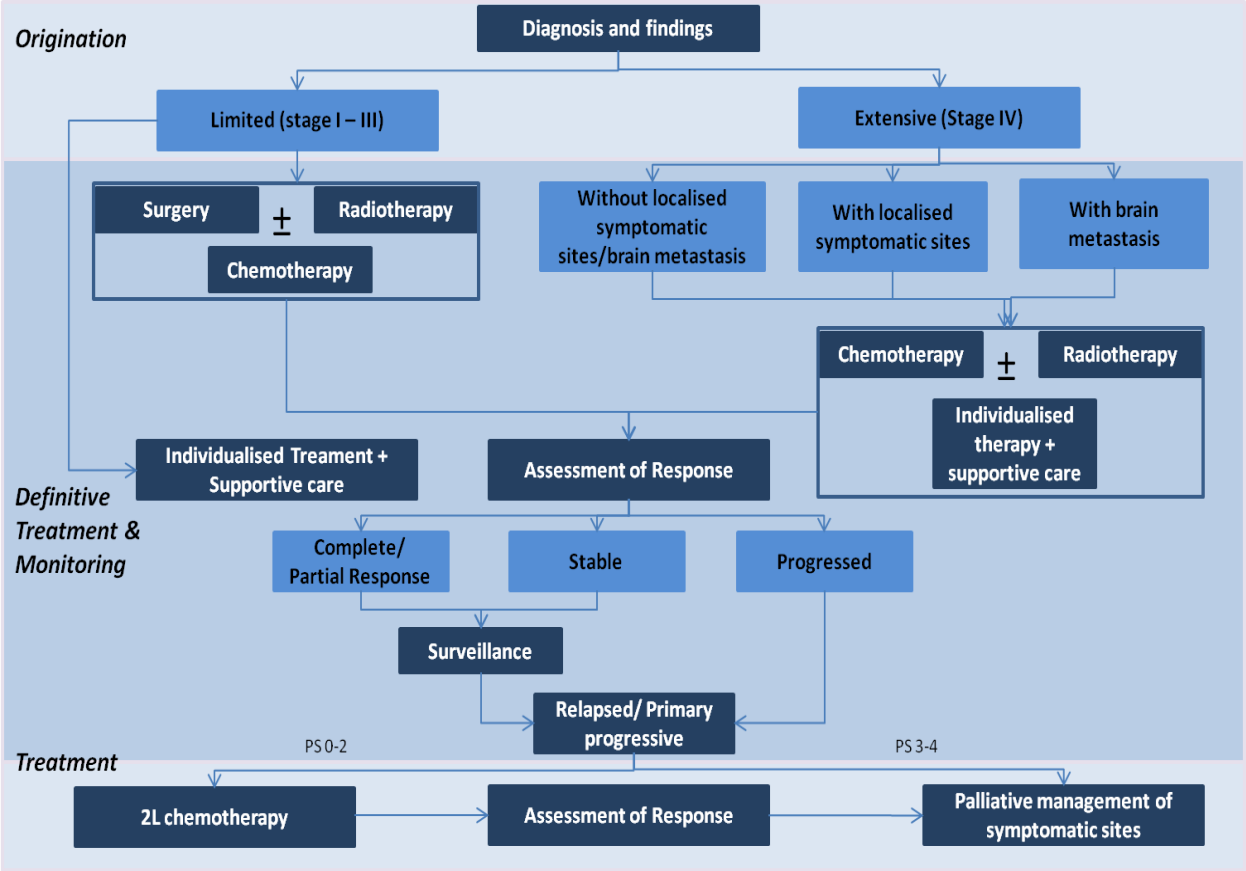

Figure 8: SCLC Treatment Flow

Sales and Market Share by Product:

Please refer to the figure 2 (breast cancer analysis) on page number 19.

List of Products:

Marketed		
Product	**Mechanism of Action**	**Company**
Tarceva (erlotinib)	EGFR Inhibitors	GNE
Gilotrif	EGFR Inhibitors	BI
Avastin (bevacizumab)	VEGFR Inhibitors	GNE
Cyramza (ramucirumab)	VEGFR Inhibitors	Eli Lilly
Zalkori (crizotinib)	ALK Inhibitors	Pfizer
Zykadia (ceritinib)	ALK Inhibitors	Novartis

Table 10: List of Marketed Products for Lung Cancer

Pipeline		
Product	**Mechanism of Action**	**Company**
Necitumumab	EGFR Inhibitors	Eli Lilly
Cetuximab	EGFR Inhibitors	Eli Lilly/ BMS
AZD9291	EGFR Inhibitors	AstraZeneca
Nintedanib	VEGFR Inhibitors	BI
MPDL3280A	PD-1 Inhibitors	Roche
Nivolumab	PD-1 Inhibitors	BMS
Pembrolizumab	PD-1 Inhibitors	Merck & Co
Alectinib	ALK Inhibitors	Roche
Custirsen	Clusterin Inhibitors	TEVA Pharma
Abemaciclib	Cyclin D Kinase 4/6 Inhibitors	Eli Lilly
Veliparib	PARP Inhibitors	AbbVie

Table 11: List of Pipeline Products for Lung Cancer

Clinical Product Comparison - Drugs available in the market:

		Tarceva *(Erlotinib)*	Xalkori *(Crizotinib)*	Gilotrof *(Afatinib)*	Zykadia *(Ceritinib)*	Avastin *(bevacizumab)*	Cyramza *(Ramucirumab)*
Indication	1L	EGFR+	Alk+	EGFR+		Metastatic	
	2L	EGFR+	Alk+		Alk+	Metastatic *	Metastatic
	3L	EGFR+	Alk+				
MOA		EGFR Inhibitors	Alk Inhibitors	EGFR Inhibitors	Alk Inhibitors	VEGF Inhibitors	VEGFR-2 Inhibitors
Efficacy	OS	6.7 – 22.9 months	20,3 months			12.3 months	10.5 months
	PFS	2.3 – 10.4 months	7.7 months	11.1 months		6.2 months	4.5 months
	ORR				54.6%		
	MRD				7.4 months		
Risk Factors		• Renal insufficiency • GI perforations • Hepatotoxocity	• Hepatotoxicity • Pneumonitis	• Stomatitis • Mucotitis • Rash	• Hepatotoxicity • Pneumonitis • GI toxicity	***Black box warning*** • GI perforations • Hemorrhage	***Black box warning*** • Hemorrhage • Hypertension • GI perforations

Figure 9: Lung Cancer Product Comparison

Key Clinical Trials - NSCLC:

Trial Name	Company	Patient Population	Key Comparators	Primary Endpoints	Expected Primary completion date
PACIFIC (MEDI4736 – Ph III)	AstraZeneca	Stage III unresectable NSCLC	MEDI4736	Overall survival	Aug 2016
			Placebo		
ARCTIC (MEDI4736 – Ph III)		Locally advanced or metastatic NSCLC	MEDI4736	Overall survival	Mar 2017
			Vinorelbine/Gemcitabine/ Erlotinib		
FLAURA (AZD9291 – Ph III)		EGFR+, Locally advanced or metastatic NSCLC	AZD9291 + Erlotinib /Gefitinib	Progression free survival	May 2017
			Placebo + Erlotinib /Gefitinib		
AURA3 (AZD9291 – Ph III)		Locally advanced or metastatic NSCLC	AZD9291 + Chemotherapy	Progression free survival	Jun 2015
			Chemotherapy		
CHECKMATE 017 (Nivolumab – Ph III)	BMS	2L, Locally advanced or metastatic NSCLC	Nivolumab	Overall survival	Jan 2016
			Docetaxel		
CHECKMATE 026 (Nivolumab – Ph III)		Stage IV NSCLC	Nivolumab	Progression free survival	Jan 2017
			Chemotherapy		
KEYNOTE 024 (Pembrolizumab – Ph III)	Merck Sharp & Dohme Corp.	Locally advanced or metastatic NSCLC	Pembrolizumab	Progression free survival	Jun 2016
			Chemotherapy		
LUX-Lung 8 (Afatinib – Ph III)	BI	2L, Stage III – IV metastatic NSCLC	Afatinib	Progression free survival	Oct 2014
			Erlotinib		
GALAXY – 2 (Ganetespib – Ph III)	Synta Pharma	Locally advanced or metastatic NSCLC	Ganetespib + Docetaxel	Overall survival	May 2016
			Docetaxel		
ALCHEMIST (Erlotinib – Ph III)	National Cancer Institute	Stage III – IV metastatic NSCLC after surgery	Erlotinib	Overall survival	Feb 2017
			Placebo		

Figure 10: NSCLC Key Clinical Trials

Key Clinical Trials – SCLC:

Trial Name	Company	Patient Population	Key Comparators	Primary Endpoints	Expected Primary completion date
MATISSE (palifosfamide – Ph III)	Ziopharma	Extensive stage SCLC	Palifosfamide + carboplatin + etoposide	Overall survival	Jun 2015
			carboplatin + etoposide		
STAD – 1 (cisplatin + etoposide – Ph III)	NCI	SCLC	Standard fixed doses	Overall survival	Jan 2016
			Toxicity adjusted doses		
Yervoy	BMS	Extensive stage SCLC	Yervoy + carboplatin + etoposide	Overall survival	Mar 2017
			carboplatin + etoposide		

Figure 11: SCLC Key Clinical Trials

Competitive milestone:

Please refer to the figure 5(breast cancer analysis) on page number 22.

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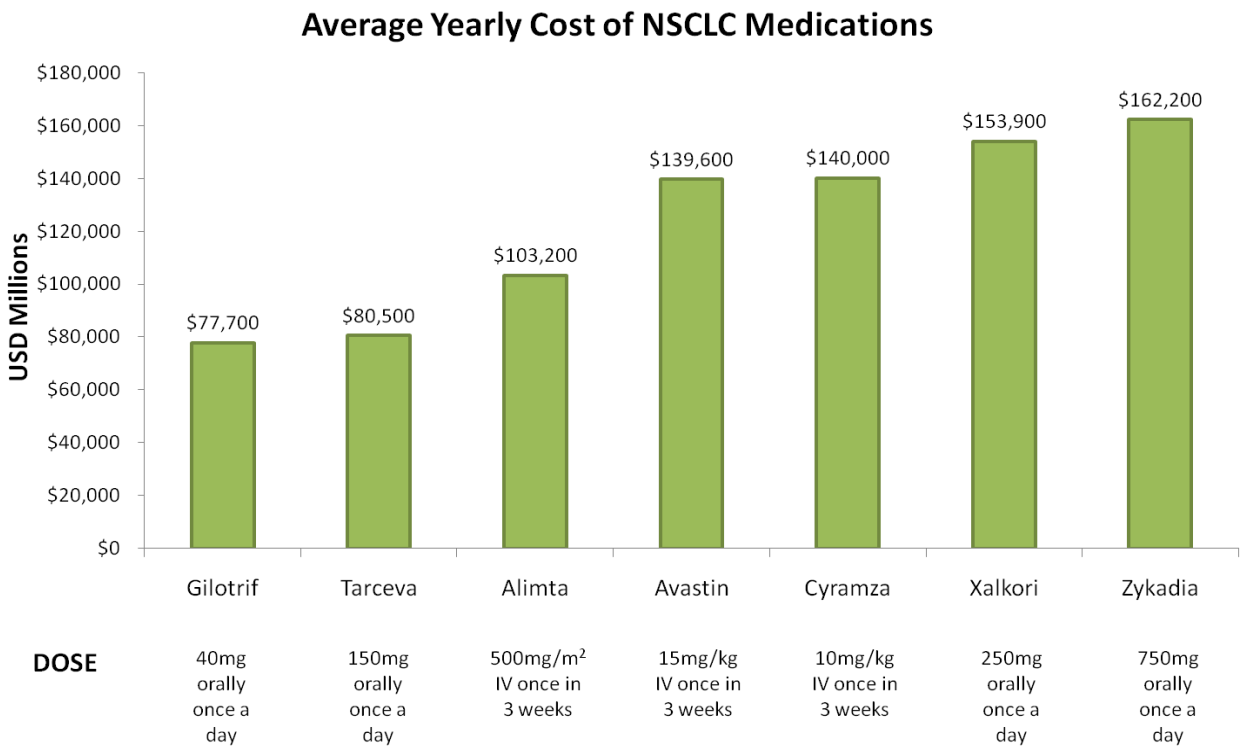

Figure 12: Average Yearly Cost of NSCLC Medications

PROSTATE CANCER

US Epidemiology:

Parameter	Data
Estimated incidence (2014)	220,800
Estimated mortality (2014)	27,540
Median age at diagnosis	66 years
Median age at death	80 years
Age adjusted incidence rates (2011)	135.74/100,000 men
Age adjusted death rates (2011)	20.77/100,000 men
Overall 5 year survival (2004-2010)	98.9%

Table 12: Prostate Cancer Epidemiology

Types of Classification of Prostate Cancer:

7. Based on stage of diagnosis:

Stage	Stage distribution	5-yr survival rate (%)
Localized	81	100
Regional	12	100
Distant	4	28
Unknown	3	74

Table 13: Prostate Cancer Classification

8. Based on risk stratification:

Stage	Serum PSA level	Gleason score	T stage
Very low	≤4 ng/ml	1-6	T0
Low	4 – 10 ng/ml	1-6	T1
Intermediate	10-20 ng/ml	7-8	T1
High	≥20 ng/ml	8-9	T1
Very high	≥20 ng/ml	9-10	T2-T3

Table 14: Prostate Cancer Risk Stratification

The risk recurrence can be calculated with nomo-grams based on serum PSA, gleason score and T stage.

9. Based on anatomic stage: (on the basis of TNM staging of cancer)
    - Stage I
    - Stage IIa and IIb
    - Stage III
    - Stage IV

Treatment Flow:

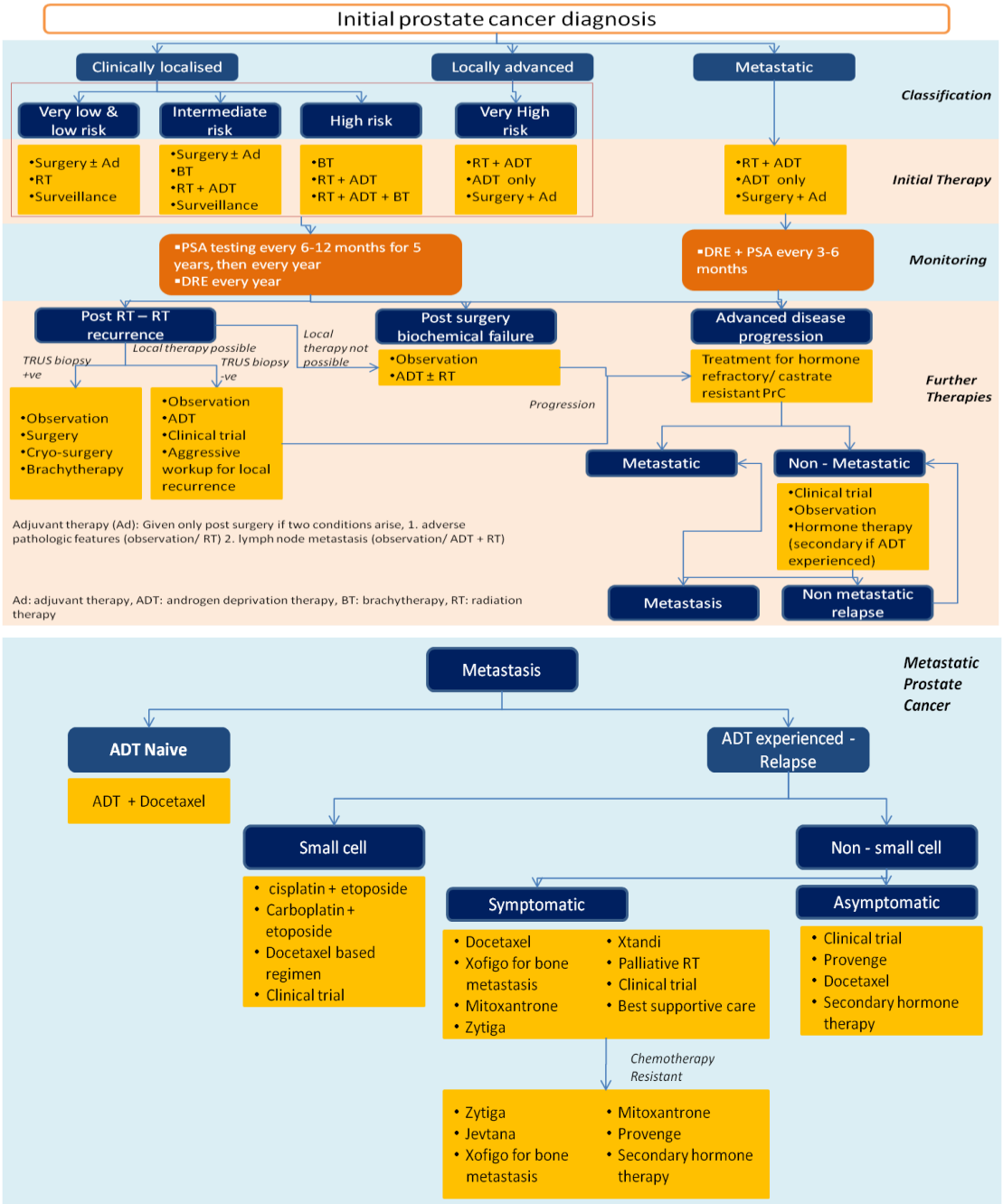

Figure 13: Prostate Cancer Treatment Flow

Sales and Market Share by Product:

Please refer to the figure 2 breast cancer analysis) on page number 19.

List of Products:

Marketed		
Product	**Mechanism of Action**	**Company**
Zytiga	CYP17A inhibitors	J&J
Xtandi	Androgen inhibitors	Astellas Pharma
Provenge	CTLA4 inhibitors	Dendreon
Xofigo	Alpha particle emitting	Fierce Pharma
Jevtana	Microtubule inhibitors	Sanofi
Taxotere	Microtubule inhibitors	Sanofi

Table 15: List of Marketed Products for Prostate Cancer

Pipeline		
Product	**Mechanism of Action**	**Company**
Masitinib	PGDFR inhibitors	AB Sciences
ARN-509	Androgen receptor signaling inhibitors	J&J
Custirsen	Clusterin inhibitors	TEVA Pharma
Ipilimumab	CTLA4 inhibitors	BMS
ProstVac	PSA-T lymphocyte stimulants	Bavarian Nordic
ProstAtak	Viral gene therapy	Advantagene
DCVAC/PCa	Stem cell therapy	SOTIO Group
Galeterone	Androgen receptor antagonist	Tokai Pharma
Buparlisib	PI3K inhibitors	Novartis
Olaparib	PARP Inhibitors	AstraZeneca
Apatorsen	HSP27 inhibitors	OncoGenex

Table 16: List of Pipeline Products for Prostate Cancer

Clinical Product Comparison – Drugs available in the market:

	LHRH Agonists (Lupron, Zoladex)	Zytiga	Xtandi	Provenge	Xofigo	Jevtana	Taxotere
Indication	First line	Metastatic CRPC	Metastatic CRPC	First line for asymptomatic	Second line after chemotherapy	Second line after chemotherapy	First line chemotherapy
Mechanism of action	Hormone agonists	CYP17A inhibitors	Androgen inhbitors	CTL4 inhibitors (immunotherapy)	Alpha particle emitting	Microtubule inhibitors	Microtubule inhibitors
Risk factors	• Increased levels of testosterone • Bone pain	• Mineralocorticoid excess • hepatotoxicity	• Seizure	• Cardiotoxicity • Hepatotoxicity	• Bone marrow supression	• Neutropenia • Hypersensitivity	• Neutropenia • Hypersensitivity • Hepatotoxicity

Table 17: Prostate Cancer Product Comparison

Identification of Key Clinical Trials:

Trial Name	Company	Patient Population	Key Comparators	Primary Endpoints	Expected Primary completion date
PROSPECT (ProstVac – Ph III)	Bavarian Nordic, Inc	Asymptomatic or minimally symptomatic CRPC	ProstVac + GM-CSF	Overall survival	Dec 2015
			ProstVac + Placebo		
			Placebo + Placebo		
ARAMIS (ODM-201 – Ph III)	Bayer	High risk non metastatic castration resistant prostate cancer	ODM-201	Disease free survival	Mar 2018
			Placebo		
SPARTAN (ARN-509)	Argon Pharma/ J&J	non metastatic castration resistant prostate cancer	ARN-509	Disease free survival	Dec 2016
			Placebo		
SYNERGY (Custirsen – Ph III)	OncoGenex	CRPC already received ADT	Custirsen + docetaxel + prednisone	Overall survival	Feb 2014
			docetaxel + prednisone		
AFFINITY (Custirsen – Ph III)	OncoGenex	CRPC, second line	Custirsen + cabazitaxel + prednisone	Overall survival	Dec 2015
			cabazitaxel + prednisone		
PACIFIC (Apatorsen – Ph II)	OncoGenex	CRPC, second line	Apatorsen + standard therapy	Progression free survival	Jun 2015
			Standard therapy		

Figure 14: Prostate Cancer Key Clinical Trials

Competitive milestone:

Please refer to the figure 5 (breast cancer analysis) on page number 22.

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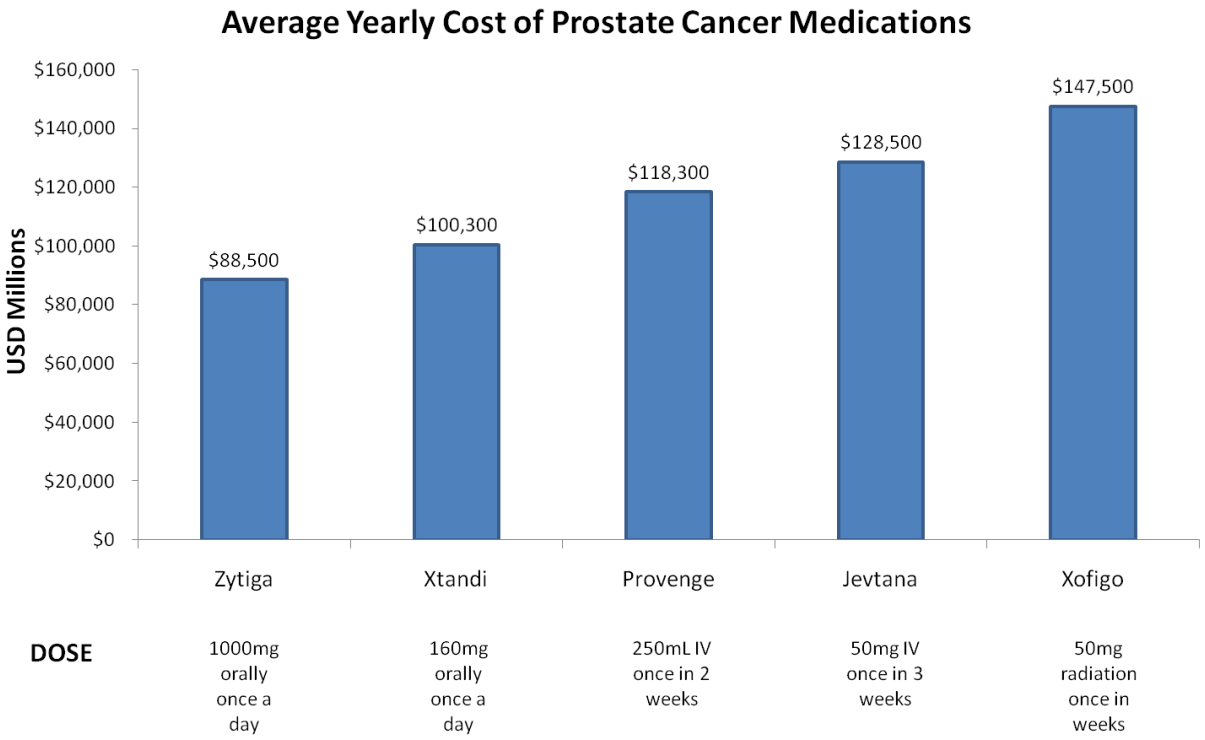

Figure 15: Average Yearly Cost of Prostate Cancer Medications

MELANOMA

US Epidemiology

Parameter	Data
Estimated incidence (2014)	73,870
Estimated mortality (2014)	9,940
Median age at diagnosis	62 yrs
Median age at death	69 yrs
Age adjusted incidence rates (2011)	21.3/100,000/yr
Age adjusted death rates (2011)	2.7/100,000/yr
Overall 5 year survival (2004-2010)	91.3%

Table 18: Melanoma Epidemiology

Types of Classification of Melanoma:

10. Based on stage of diagnosis:

Stage	Stage distribution	5-yr survival rate (%)
Localized	84%	98.1%
Regional	9%	62.6%
Distant	4%	16.1%
Unknown	3%	78.3%

Table 19: Melanoma Classification

11. Based on anatomic stage: (on the basis of TNM staging of cancer)
    - Stage 0
    - Stage I
    - Stage II
    - Stage III
        - Micrometastases
        - In transit disease
        - Macrometastases
    - Stage IV

12. Breslow Classification:
    - It is a thickness based classification. In this type of classification, cancer is classified on the basis of the thickness of lesion. Higher the breslow thickness, worse is the prognosis. Due its accuracy in predicting outcomes, the breslow thickness has been incorporated into the standard TNM staging system for melanoma. Usually, thin melanomas are associated with localized disease, intermediate melanoma with regional and/or distant metastasis and thick melanomas with distant metastases at time of initial presentation.
    - Thin melanoma (0.75mm or less)
    - Intermediate melanoma (0.76mm – 1.75mm, 1.76mm – 4mm)
    - Thick melanoma (More than 4mm)
13. Based on Growth pattern:
    - Superficial spreading
    - Nodular
    - Lentigo maligna
    - Acral lentiginous

14. Based on site of origin:
    - Skin without chronic sun damage
    - Skin with chronic sun damage
    - Mucosal surfaces
    - Uveal melanoma
    - Acral surfaces

15. Based on driver mutation:
    - BRAF (50%)
    - MEK1 (6%)
    - CTNNB1 (2-3%)
    - NRAS (13-25%)
    - KIT (2-6%)

Treatment Flow:

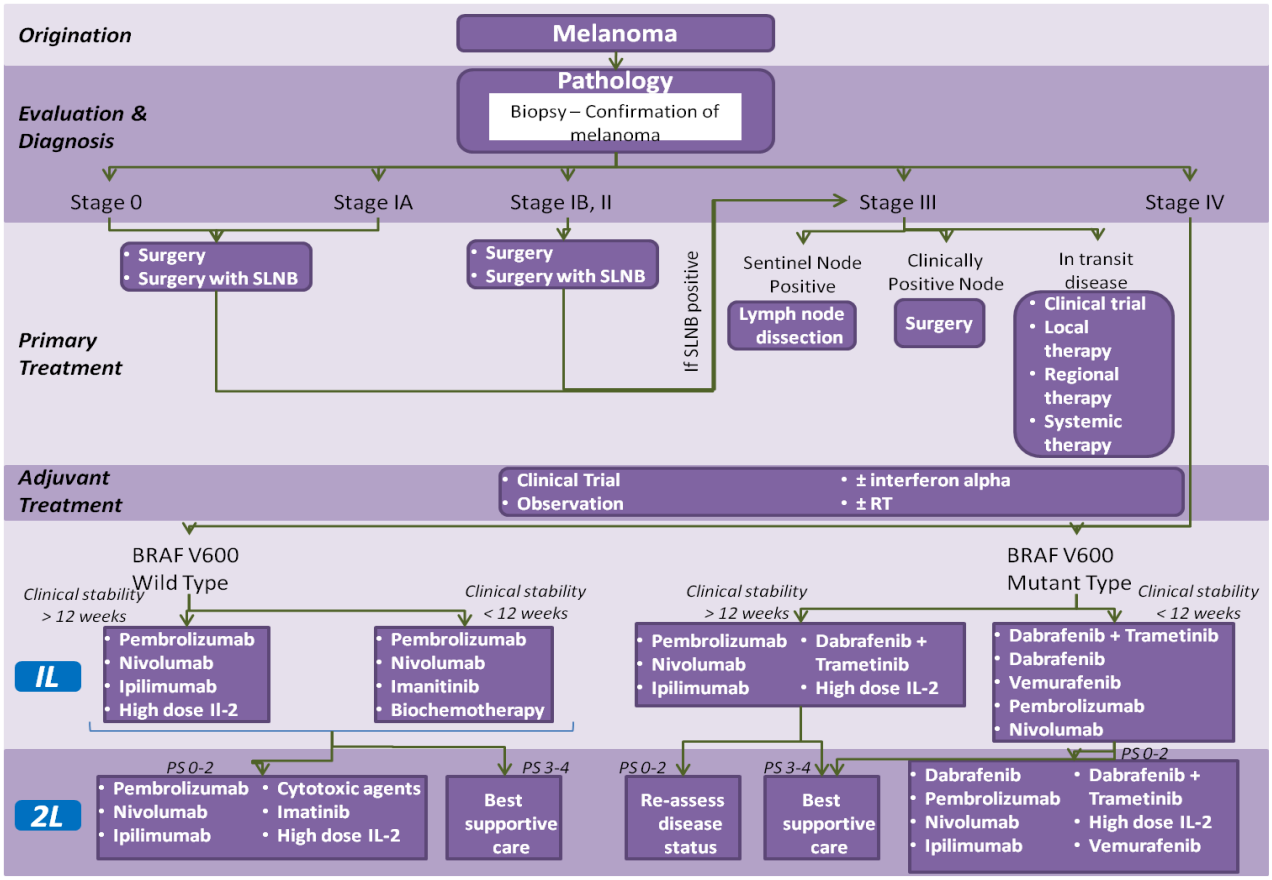

Figure 16: Melanoma Treatment Flow

Sales and Market Share by Product:

Please refer to the figure 2(breast cancer analysis) on page number 19.

List of Products:

Marketed		
Product	**Mechanism of Action**	**Company**
Yervoy	CTLA-4 inhibitors	BMS
Keytruda	PD-1 inhibitors	Merck & Co
Opdivo	PD-1 inhibitors	BMS
Zalboraf	BRAF inhibitors	Roche
Tafinlar	BRAF inhibitors	GSK
Mekinist	MAPK inhibitors	GSK

Table 20: List of Marketed Products for Melanoma

Pipeline		
Product	**Mechanism of Action**	**Company**
Encorafenib	BRAF inhibitors	Novartis
Cobimetinib	MAPK inhibitors	Roche
Binimetinib	MAPK inhibitors	Novartis
Seviprotimul-L	Immunostimulants	Polynoma
Eltrapuldencel-T	Immunostimulants	Neostem, Inc
M-VAX	Immunostimulants	AVAX Technologies
T-VEC	Immunostimulants	Amgen
MAGE-A3	Immunostimulants	GSK
Ramucirumab	VEGFR inhibitors	Eli Lilly
Pidlizumab	PD-1 inhibitors	Medivation

Table 21: List of Pipeline Products for Melanoma

Clinical Product Comparison – Drugs available in the market:

		Interleukin – 2	Yervoy *(ipilimumab)*	Keytruda *(pembrolizumab)*	Opdivo *(nivolumab)*
Indication	1L	Metastatic	Metastatic	Metastatic *	Metastatic *
	2L	Metastatic	Metastatic	Metastatic	Metastatic
	3L				
MOA		IL – 2 receptor agonists	CTLA 4 inhibitors	PD-1 Inhibitors	PD – 1 Inhibitors
Efficacy	OS	33.3 months, 21 months (stable disease)	10 months	-	-
	PFS		-	-	-
	RFS		-	-	-
	ORR	16%	5.7%	24%	32%
	MRD	9 months	11.5 months		
Risk Factors		***Black box warning*** • Capillary leak syndrome • Impaired neutrophil function • coma	***Black box warning*** • Enterocolitis • Dermatitis • Neuropathy • Hepatitis	• Pneumonitis • Hepatitis • Nephritis • Embryofetal toxicity	• Pneumonitis • Hepatitis • Nephritis • Embryofetal toxicity

OS: overall survival, PFS: progression free survival, RFS: relapse free survival, ORR: objective repsonse rate, MRD: median response duration
* : not approved by FDA but recommended by NCCN

Figure 17: Melanoma Product Comparison

		Zelboraf (vemurafenib)	Tafinlar (dabrafenib)	Mekinist (trametinib)
Indication	1L	BRAF +	BRAF +	BRAF +
	2L	BRAF +		BRAF +
	3L			
MOA		BRAF inhibitors	BRAF inhibitors	MAP kinase inhibitors
Efficacy	OS	13.6 months		
	PFS	5.3 months	5.1 months	4.8 months
	RFS			
	ORR	2L: 52%	• Monotherapy – 52% •Combination with Mekinist: 41%	• Monotherapy: 22% • Combination with Tafinlar: 41%
	MRD	2L: 6.5 months	• Monotherapy: 5.6months • Combination: 10.5 months	• Monotherapy: 5.5 months • Combination: 10.5 months
Risk Factors		• New primary malignancies • Hepatotoxicity • Photosensitivity • Embryofetal toxicity	• New primary malignancies • Haemorrhage • Cardiomyopathy • Embryofetal toxicity	• New primary malignancies • Haemorrhage • Cardiomyopathy • Embryofetal toxicity

OS: overall survival, PFS: progression free survival, RFS: relapse free survival, ORR: objective repsonse rate, MRD: median response duration
* : not approved by FDA but recommended by NCCN

Figure 17 Continued: Melanoma Product Comparison

Identification of Key Clinical Trials:

Trial Name	Company	Patient Population	Key Comparators	Primary Endpoints	Expected Primary completion date
CHECKMATE 066 (ph – III)	BMS	1L , unresectable BRAF+ stage III-IV melanoma	Nivolumab + Placebo Dacarbazine + Placebo	Overall survival	Jun 2014
CHECKMATE 069 (ph II)		1L , unresectable BRAF+ stage III-IV melanoma	Nivolumab + Ipilimumab & Nivolumab Placebo + Ipililimumab & placebo	Objective response rate	Jul 2014
Vemurafenib (Ph II)		1L , unresectable BRAF+ stage IV melanoma	Vemurafenib followed by ipilumumab Ipilimumab followed by vemurafenib	Grade 3-4 adverse events	Jul 2014
CHECKMATE 067 (Ph III)		IL, stage III or IV melanoma	Nivolumab + Placebo Nivolumab + Ipilimumab	Overall survival	Sep 2016
KEYNOTE 006 (Ph III)	Merck Sharp & Dohme Corp.	IL, stage III or IV melanoma	Pembrolizumab Ipilimumab	Progression free survival	Mar 2015
BRIM8 (Ph III)	Hoffmann – La Roche	Adjuvant, resectable and high rosk melanoma	Vemurafenib placebo	Disease free survival	Jun 2016
COMBI – AD (Ph III)	GSK	Adjuvant, resectable and high risk melanoma	Dabrafenib + Trametanib Placebo	Disease free survival	Jul 2015
COMBI - V		1L, BRAF+ stage III – IV melanoma	Vemurafenib Dabrafenib + Trametanib	Overall survival	Sep 2018

Figure 18: Melanoma Key Clinical Trials

Competitive milestone:

Please refer to the figure 5 (breast cancer analysis) on page number 22.

Pricing:

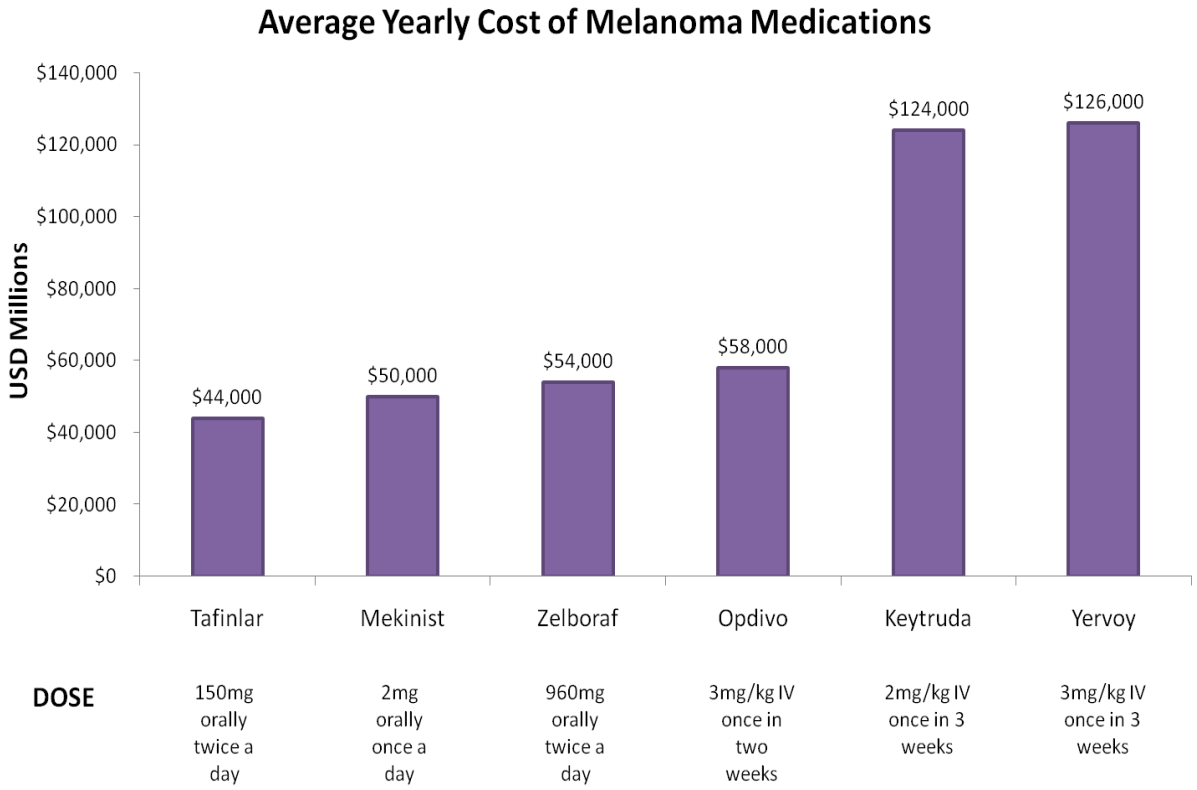

Figure 19: Average Yearly Cost of Melanoma Medications

DISCUSSION AND CONCLUSION

BREAST CANCER

Breast cancer is the most common cancer in the USA with the highest incidence and mortality. However, five year survival rate has improved over the years due to availability of better treatment options in the face of targeted therapies.

Of all the types of breast cancer, hormone positive is the most common type as 55% of the breast cancer patients are hormone positive.

Due to improved diagnostic testing and awareness among individuals, 60% of the patients are identified at Stage I and Stage II of breast cancer.

Once the patient presents to the physician with signs and symptoms, diagnosis is confirmed and then staging is done. Treatment is currently determined based on hormone-receptor and HER2 expression, and successful therapies are often those tailored to specific subpopulations. Prior to surgery, neoadjuvant treatment is provided with a goal to downstage the tumor and increase the likelihood of response. Post surgery, adjuvant treatment is provided with an aim to reduce the chance of recurrence. If the disease progresses after primary treatment, then metastatic treatment is provided with an intention of palliative care. Metastatic treatment has various options of monotherapies and combination therapies chemotherapy.

The breast cancer is anticipated to be led by oral targeted therapies like Ibrance and Tykerb. According to findings from Decision Resources Group, sales of breast cancer therapies are expected to almost double through 2023, fueled by growth in several distinct market segments.

A number of products are already available in the market; however, owing to its large population, the treatment of breast cancer remains an active area of research with a rich and diverse product pipeline. A competitive current therapies market means that barriers to entry are high, and relatively few of the many therapies in development will enter this lucrative market.

The most awaited products in the pipeline are CDK4/6 inhibitors and PARP inhibitors. Palbociclib, CDK 4/6 inhibitor is now even recommended by NCCN guidelines. A subset of breast cancers harbors germ line BRCA1/2-mutations, and the PARP inhibitor drug class has emerged as a potential targeted therapy for this population. Four PARP inhibitors are now in Phase III development; Tesaro's niraparib, BioMarin's BMN-673, AstraZeneca's olaparib and AbbVie's veliparib—however, forecasted sales of these agents arising from the BRCA1/2-mutated breast cancers are limited by the small size of the BRCA1/2-mutated population.

Identification of key clinical trials indicates that the breast cancer drug development is a hive of activity and has a very busy pipeline.

The next couple of years are crucial and busy due to a number of product launches.

Although the targeted therapies are more effective and user friendly, they are expensive and mostly cost more than $60,000 for a year.

LUNG CANCER

Although lung cancer is ranked third in incidence, it is one of the most fatal types of cancer and has a poor 5 year survival rate of nearly 17% only. It is the leading cause of deaths in the world. Most of the cases of lung cancer are of non small cell lung cancer type (around 85%) and remaining is of small cell lung cancer type. Among all the types of driver mutations, KRAS, EGFR and ALK, mutations are the most common. Lung cancer is usually detected a bit late and thus most of the patients are identified once they reach stage III or beyond.

Treatment has shown a shift from radiation and chemotherapy to the use of targeted therapies. There is a rapidly growing understanding of genetic profiling for lung cancer. Therapies targeting EGFR and ALK are already being used. Targeted therapies control the tumor growth, though continued usage leads to the development of resistance. Goal for the future is to discover more rational combinations for complete tumor response.

The lung cancer market is expanding rapidly, from $2.6 billion in 2009 to $4.8 billion in 2016. Avastin was the first targeted therapy that was launched in 2006 and since then it has continued to dominate the market. PD-1 inhibitors (nivolumab and pembrolizumab) are expected to drive the market and gain one third of the market by 2020.

Pipeline products aim to target mutations other than EGFR and ALK like KRAS, HER2, BRAF, PD-1 inhibitors show promising data and are undergoing phase III trials. Even novel therapies like CDK 4/6 inhibitors and PARP inhibitors are being tried and are currently in the late stage of development. However, in case of small cell lung cancer, there is not much of development and the pipeline is also not very busy.

Competition in the market is expected to increase surely with different therapies entering the market and competing for the same target population. Nevertheless, the timeline for launches is not very busy in the coming couple of years.

The treatment cost of NSCLC is very high ranging from $77,000 to $162,000, thus affecting the overall acceptance of the treatment by the patients.

PROSTATE CANCER

Prostate cancer is the most common non - cutaneous cancer in men in USA. Despite that, the five year survival rate for prostate cancer is quite high (around 98%) which is remarkable in comparison to other oncology indications. In the past couple of decades, the incidence of prostate cancer has increased substantially and this can be arguably attributed to increase testing and diagnosis through PSA testing that had been launched in the late 1980s and early 1990s.

The current anti-hormonal therapies used for the treatment for the hormones-sensitive prostate cancer are quite effective and provide adequate disease control for many years but unmet needs exist in metastatic and non-metastatic castration resistant prostate cancer where most anti-hormonal drugs are ineffective. The pharma options used are hormonal therapies that either slow down the androgen levels or stop androgen from working.

The global prostate cancer drug market is increasing, driven by aging population and by the growth in the hormone refractory prostate cancer therapeutics market. It is expected to reach $18.6 billion in 2017, with a compounded annual growth of 11.4%.

Significant development and approvals have happened in the last 5 years. Currently, J&J's Zytiga and Astellas Pharma's Xtandi are the forerunners in the treatment of mCRPC competing fiercely for market share.

Recent approval of both zytiga and xtandi in the chemo-naïve patient setting is already changing the treatment paradigm, relegating the erstwhile first-line standard of care docetaxel to later lines of therapy.

The current stage pipeline has many immunotherapeutic agents and targeted therapies with little developmental activities seen in cytotoxic or anti-hormonal class. However, there are no immediate launches in the next couple years in prostate cancer market.

The non-metastatic CRPC, an untapped market has also intensified with many agents (Xtandi, ARN-509, ODM-201) being evaluated in Phase III trials.

The recent launches in the market are driving the cost up of prostate cancer treatment be it targeted therapies or immunotherapies to up to $128,500 a year.

MELANOMA

The mortality due to melanoma is not very high but it has a high incidence in USA. However, the number of incident malignant melanoma cases in the USA is expected to increase by 50% between 2013 and 2033. The overall 5 year survival rate is also high, round 90%. The most common driver mutation for melanoma is BRAF and 50% of melanoma patients show this type of genetic mutation.

The incidence of malignant melanoma is relatively low compared with that of many other malignancies, such as breast cancer or prostate cancer, and few patients are diagnosed with unresectable or metastatic disease. However, the prognosis for unresectable or metastatic patients is extremely poor, as exemplified by a five-year survival rate of approximately 15%

for patients with stage IV disease. Until recently, therapeutic options for malignant melanoma were severely limited and remained relatively unchanged.

The treatment of melanoma is based on the type of genetic mutation. While considerable advances have been made with the approval and ongoing launch of these new agents, there remains significant need for more effective treatments that prolong patient survival. To this end, several emerging agents hope to compete in the malignant melanoma market by the end of 2015. Furthermore, the launch of BRAF and MEK inhibitors for BRAF-mutation-positive melanoma has segmented the market according to patients' BRAF-mutation status, a trend that looks set to continue. With the entry of novel immunotherapies and BRAF and MEK inhibitors, the melanoma market is set to become increasingly competitive as agents vie for patient share.

Amongst immunotherapeutic agents, PD-1 inhibitors will have the largest market share in the future due to considerable efficacy with impressive safety and tolerability profiles. Mekinist is anticipated to be the forerunner among all the targeted therapies available in the future.

The pipeline is heavily occupied by immunostimulants and the market is expected to become more competitive due to similar performing products being launched in the market. The future of melanoma treatment is clearly going to be in combinations, both for targeted therapy and for immunotherapy. There must be at least 20 such combination trials in the pipeline.

Melanoma treatment cost varies by phase of care and stage at diagnosis; costs are highest among patients diagnosed with late stage disease and in the initial and terminal phases of care. Yervoy has the highest cost of therapy despite that is occupies a large market share. With the launch of Opdivo and Keytruda, the patients will have a suitable cost effective option for treatment.